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EXAMINER	
MOORE, WILLIAM W	
ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/884,456	HOUGHTON ET AL.	
	Examiner	Art Unit	
	William W. Moore	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed on 31 October 2007 in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 FR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 31 October 2007 has been entered. Claims 27-44 were not amended and remain in the application.

Double Patenting: Non-Statutory

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 27-44 remain rejected for reasons of record under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 5,371,017.

Claims 27-43 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, 8-12, 14 and 15 of copending application 10/438,313. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

While Applicant states at page 5 of the Response filed 31 October 2007 [Response hereinafter] that (a) terminal disclaimer(s) will be filed to overcome both rejections of record herein upon an indication of allowable subject matter herein, these rejections must be maintained until and unless an effective terminal disclaimer is filed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make

> and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-44 remain rejected for reasons of record under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant's arguments at pages 5-16 of the Response have been fully considered but are not deemed to be persuasive to overcome the rejection of record. Applicant suggests at page 6 therein that the communication mailed 2 May 2007 had not "set out a prima facie case of [a] lack of [adequate] written description" and points out that that the particular appellate decision first cited at page 6 of the communication mailed 9 July 2004, had not been specifically cited in the most recent communication mailed 2 May 2007. Since the decision is particularly pertinent to analysis of the presence or absence of an adequate written description in inventions in the art of biotechnology, it is again noted that

> "While one does not need to have carried out one's invention before filing a patent application, one does need to be able to describe that invention with particularity" to satisfy the description requirement of the first paragraph of 35 U.S.C. §112. *Fiers v. Revel v. Sugano,* 25 USPQ2d 1601, 1605 (Fed. Cir. 1993).

The Federal Circuit is thus considered to have enunciated a **principle** guiding the analysis of the facts presented by the instant specification, rather than a rule, in a decision involving the state of the art in biotechnology at a time equivalent to the 4 April 1991 filing of the present disclosure. The Federal Circuit earlier indicated that the "test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the . . . claimed subject matter", *In re Kaslow*, 217 USPQ 1089, 1096 (Fed. Cir. 1983). Applicant also suggests that the USPTO Guidelines for analysis of compliance with the written description requirement cannot supplant application of the law established by appellate decisions.

The Guidelines do not set aside factual analysis as a basis for determining whether the statutory requirement is met. They instead require a factual analysis of the presence in, or absence from, the specification of an adequate written description of the **claimed** subject matter, stating that an applicant may comply with the written description requirement by showing that an "invention is **complete** by disclosure of **sufficiently detailed, relevant identifying characteristics** . . . i.e., complete or partial structure, other physical and/or chemical properties, function characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." **Guidelines**, 66 Fed. Reg. 1099 at 1106 (5 January 2001) (emphasis supplied). The Federal Circuit adopted the USPTO's standard for determining compliance with the written description requirement in a decision in the

biotechnological arts, *Enzo Biochem Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 (Fed. Cir. 2002). As discussed in the written description guidelines, the written description requirement for a claimed genus may be satisfied through (i) a sufficient description of a representative number of species by actual reduction to practice, (ii) a reduction to drawings, (iii) a disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, (iv) by functional characteristics coupled with a known or disclosed correlation between function and structure, or (v) by a combination of such identifying characteristics sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species which are adequately described are representative of the entire genus. Thus, a sufficient variety of species must be described that reflect the variation within a genus where there is substantial variation within the genus. Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that an applicant had possession of the necessary common attributes or features of elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus embracing widely variant species cannot be achieved by disclosing one species within the genus.

Applicant suggests at page 7 of the Response that the specification adequately discloses compositions comprising polynucleotides that encode "an NS3 domain hepatitis C virus [HCV] protease that corresponds to" a "NS3 domain serine protease activity" and comprises "the entire domain required for [a] NS3 serine protease", as well as disclosing "substrates for assay its activity". Applicant asserts that the comprised polynucleotides are equally disclosed to provide a NS3 domain protease that has NS2/3 protease activity – which is not serine protease activity as the subsequent art of record herein has since shown. The rejected claims 27-44 that the specification should somewhere adequately support are drawn to polynucleotides (i) encoding "an HCV NS3 domain protease or an active HCV NS3 domain protease truncation analog" or (ii) encoding fusion polypeptides comprising such an "HCV NS3 domain protease" or an "active HCV NS3 domain protease truncation analog". Applicant's argument suggests that at least an HCV NS3 domain protease, whether or not it is fused to a non-HCV protein, might provide either of two, alternative, proteolytic activities, and that truncation analogs may have a series of successively smaller partial internal amino acid sequences, e.g., SEQ IDs NOs:63, 64, or 65. These products are members of broad genera because the best-defined among them, the 202-amino acid sequence of SEQ ID NO:65 of claims 28 and 31 (note that SEQ ID NO:1 is also SEQ ID NO:65), is the species having the most extensive structure. Thus the genus of encoded amino acid sequences of larger NS3 domain proteases might vary to any conceivable extent

beyond the amino-terminal and carboxy-terminal boundaries of SEQ ID NO:65. The genera of polynucleotides encoding polypeptides comprising SEQ IDS NOs:63 and 64 - respectively, a undecapeptide within SEQ ID NO:65 and a separate, non-contiguous, nonapeptide within SEQ ID NO:65 – are broader still since only a minimal structure is required, while the genera of protease-encoding polynucleotides indicated in recitations of claims 27, 32, 33, and 37 are even broader genera where they admit the alteration of any number of positions within, as well as beyond, the 202-amino acid sequence of SEQ ID NO:65. See page 9, line 7, through page 11, line 9, of the specification.

If Applicant believes that the specification discloses a representative number of species that correspond to any of the increasingly broader genera embraced by the claims, the arguments made 31 October 2007 do not indicate where such species are disclosed in the specification. Furthermore, the claims require no particular activity of an encoded protease, not even that of a NS3 domain serine protease nor that of a NS2/3 region autocatalytic metalloprotease, because the claims state no substrate or class of substrates. The most particular substrates disclosed in the specification, at pages 19-21, are peptides comprising at least two consecutive arginines, the three particular peptides set forth in SEQ IDs NOs:36, 88, and 89, and the HCV polyprotein. Polynucleotides of the rejected claims, though, encode polypeptides with any protease activity.

Applicant does not argue that the specification discloses a number of species adequate to demonstrate that Applicant indeed possessed any of the broad genera indicated in the claims. Applicant argues instead at pages 7-8 of the Response that the specification discloses at least one "NS3 domain" having "a NS3 serine protease activity" and points to the "Office Action at pages 5-6" for agreement with this proposition. The language Applicant cites does not appear anywhere in the communication mailed 2 May 2007 and is instead a quote abstracted from the specification at the close of page 5 of the communication mailed 12 January 2006. This quote frames a discussion of the Declarations under 37 CFR 1.132 submitted 12 February 2007 which concludes that the Declarations provide no corroboration that the events reported in Example 5 of the specification actually show a proteolytic activity by any of the fusion polypeptides disclosed in the specification. Applicant recapitulates the arguments made in the Response filed 12 February 2007 but argues limitations not found in the claims, which remain unamended. Applicant's reliance on the later publication of Bartenschlager et al., 1994, to demonstrate the adequacy of written disclosure in the specification is unpersuasive. This is because (1) the specification does not disclose or suggest a species larger than SEQ ID NO:65/SEQ ID NO:1 that is a serine protease or (2) point to a substrate recombinantly expressed by Applicant and identifiable in the specification that is cleaved at the carboxyl terminus of the NS3 domain, e.g.,

a NS3/NS4A cleavage, such as that reported by Bartenschlager et al. in the paragraph that spans the left and right columns at page 5050.. Arguments in the Response premised on a HCV NS/23 metalloprotease activity are likewise unpersuasive, nor can such a protease activity become a basis for amending the claims, where there is no disclosure or suggestion of this activity in the specification. As noted at page 7 of the communication mailed 2 May 2007 with respect to the events reported in Example 5 of the specification,

> "What a skilled artisan would understand from the disclosure of the specification is that the p300, p500, and p600 fusion proteins were cleaved, and that the p190 fusion protein was not cleaved, but would find no evidence therein as to the nature of the protease producing the cleavage nor even evidence of the site in the fusion protein where the cleavage occurred other than the size of the fragment on the SDS gel which fails to agree with what one would expect from a cleavage at the NS2/3 cleavage site as discussed above. Instead, the only available evidence as to what protease produced the cleavage, i.e., the size of the cleavage fragment produced, leads away from a conclusion that the cleavage was produced by a HCV NS2/3 protease."
>
> The rejection of record is therefore maintained.

Claims 27-44 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not reasonably enable the preparation of polynucleotides that encode proteins, including the P600, P500, P300 and P190 proteins, that comprise an HCV-specific protease activity, or generic versions thereof, or active truncation analogs thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicant's arguments at pages 16-22 of the Response filed 31 October 2007 have been fully considered but are not persuasive. Applicant suggests at pages 16-17 of the Response that it is necessary to provide a reason to doubt the objective truth of the statements in the specification and proposes, at pages 17-18 of the Response, that the specification should be considered to enable a NS3/3 protease where the specification discloses a polynucleotide encoding the 686-amino acid sequence of Figure 1, which is SEQ ID NO:70. Applicant implies that fusion of the encoded polypeptide with human superoxide dismutase [hSOD] might provide the autocatalytic activity of the NS2/3 protease established by publications in the art well after the filing date for the disclosure of the specification. Reasons for doubting the objective truth of the assertions of the specification are discussed at pages 7-11 of the communication mailed 12 April 2005, where it is shown that the specification's proposed working embodiment of Example 5 cannot be a credible demonstration of either NS2/3 domain boundary metalloprotease activity or NS3 substrate domain serine protease activity in view of the findings of the subsequent art. It is not clear whether Applicant is now suggesting that the encoded SEQ ID NO:70 should replace the P190, P500, and P600 fusion polypeptides or become a fusion partner with hSOD in a fusion polypeptide of the claims. In either setting, the amino terminus of SEQ ID NO:70

coincides with the amino-termini of SEQ IDs NOs:67 and 68, thus adds an additional 59 amino acids amino-proximal to the amino terminus of SEQ ID NO:65, a region that is insufficient, see pages 10 and 11 and footnotes 7 and 8 of the communication mailed 12 April 2005, to permit metalloprotease-like *cis*-cleavage at the NS2/3 boundary. While SEQ ID NO:70 adds much more structure to the carboxyl terminus of SEQ ID NO:65, 423 additional amino acids, there is no suggestion and, more importantly, no indication in the specification that Applicant expressed a polynucleotide encoding SEQ ID NO:70 that generated a NS3/4 boundary cleavage. Neither an NS2/3 nor an NS3/4 cleavage comports with the observations of cleaved products stated in Example 5 of the specification because an NS3/4 boundary cleavage would have left the hSOD fusion partner joined to almost the entire HCV NS3 domain fusion partner, producing a result of "no cleavage" as measured by Western blotting of Example 5 where any portion of a cleaved NS4 domain would have a mass insignificant to measure a difference by polyacrylamide gel electrophoresis. Thus no serine protease cleavage at the NS3/4 boundary would be detected that could support Applicant's alternative proposal at pages 18-19 of the Response.

The guidance provided by the specification is a key factor in determining whether or not a disclosure can enable the breadth of the claims and whether or not "undue experimentation" would be required to make and use an invention commensurate in scope with the claims. The CCPA, the precursor of the Court of Appeals for the Federal Circuit, determined that a **reasonable correlation** must exist between the **scope asserted** in the claimed subject matter and **the scope of the guidance** the specification provides. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 25 (CCPA 1970) (emphases supplied). The Federal Circuit approved the standard set by the CCPA in *Genentech, Inc. v. Novo-Nordisk A/S*, 42 USPQ2d 1001 (Fed. Cir. 1997). The specification consistently teaches away from any experimentation that might lead to preparation of a polynucleotide not yet described by claims rejected herein, such as Applicant's current proposal of a polynucleotide encoding SEQ ID NO:70. The only particular substrates the specification proposes, at pages 19-21, are not substrates of the NS3 domain serine protease of SEQ ID NO:65. See pages 8 and 9 of the communication mailed 2 May 2007. There is no guidance in the specification as to what more might be required beyond the amino acid sequence of SEQ ID NO:65 to locate the sequence of NS4A cofactor, a cofactor that is not present in SEQ ID NO:65 which was discovered in the art well after the date for the disclosure of the specification herein, that could bring about cleavage of the native polyprotein. See Failla et al., Ref 433, and Lin et al., Ref 601. Because the scope of guidance provided by the specification does not indicate the direction the artisan might take to begin the next, necessary, process of experimentation, the rejection of record is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 27-44 remain rejected for reasons of record under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's arguments at pages 22-25 of the Response have been fully considered but are not deemed to be persuasive to overcome the rejection of record. Applicant suggests that the recitation "HCV proteolytic polypeptide" in the independent claims 27 and 37 renders the rejected claims definite because an encoded, starting, "HCV NS3 domain protease" and any encoded, alternative, "truncation analog" must both be an "HCV proteolytic polypeptide". Thus, Applicant believes that the artisan and the public, seeking to determine the metes and bounds of the intended subject matter, need no starting point with which to distinguish between a first HCV NS3 domain protease and any of its truncation analogs, e.g., by reference to a particular drawing Figure or SEQ ID NO. Nevertheless, in arguing a limitation not present in any claim, Applicant suggests that the artisan and the public would somehow recognize the encoded amino acid sequence of SEQ ID NO:70 as the yardstick for measuring lesser included truncation analogs despite any explicit teaching, or even a suggestion, in the specification that would direct the artisan and the public to select this particular amino acid sequence. It is incumbent on Applicant to provide a definite basis for determining the metes and the bounds of the claimed subject matter, and it is agreed that the specification provides a basis for amending claims 27 and 37 to recite SEQ ID NO:70. Until and unless the claims are amended to provide a definite basis for distinguishing a first "HCV NS3 domain protease" from all lesser truncation analogs, the rejection of record of claims 27-44 must sustained.

At pages 24-25 of the Response, Applicant addresses the separate rejection of record of claims 27-31 as indefinite in view of claim 27's recitation of the phrase, "consists essentially of". Applicant renews the argument that the claims be considered to describe a "dominant [coding] component" and to encode other components, again citing *PPG Industries v. Guardian Industries*, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998). Contrary to Applicant's contention in the Response, the rejection of record noted that the compositions comprising polynucleotides of claims 27-31 **cannot** be considered compositions of matter that have "listed ingredients", or considered open to "unlisted ingredients that do not materially affect the basic and novel properties" of the stated "ingredient". This is because each rejected claim necessarily describes a polymer within which each nucleotide is covalently bonded to at least one other nucleotide, and a resulting polynucleotide can have no physically separate, lesser,

component, thus cannot "consist essentially of" one component. Note that claim 44, that also depends from claim 27, is not subject to the rejection of record where it logically, and definitely, recites the transitional phrase "encodes only". Claim 44 is, however, subject to the broader, preceding, rejection of claims 27-44. The rejection of record of claims 27-31 is sustained.

Conclusion

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 571.272.0933 and whose FAX number is 571.273.0933. The examiner can normally be reached Monday through Friday between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Primary Examiner, Dr. Kathleen Kerr Bragdon, can be reached at 571.272.0931. The official FAX number for all communications for the organization where this application or proceeding is assigned is 571.273.8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571.272.1600.

/Nashed/
Nashaat T. Nashed, Ph.D.
Primary Examiner, Art Unit 1656

William W. Moore
16 November 2007